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Influenza Vaccine: Current Status, Lessons Learned and Preparing for the Future

Statement of

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INTRODUCTION

Mr. Chairman and members of the Committee, I am Dr. Jesse Goodman, Director of the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA) and also a practicing Infectious Diseases specialist. I appreciate the opportunity to update you on FDA's recent and ongoing efforts, in collaboration with other Department of Health and Human Services (HHS) agencies and with the private sector, to address influenza vaccine needs for the current flu season and to do what we can to prevent such problems from recurring. These efforts should also help better prepare us for the next global influenza pandemic.

FDA is responsible for the regulation and oversight of vaccines in the United States. Vaccines are among our most important and cost-effective medical interventions, preventing disease in those who receive them and reducing the spread and risk of infections through our communities. I want to assure the American public that the safety, effectiveness and availability of vaccines are among FDA's highest priorities.

THE 2004-2005 INFLUENZA SEASON

As you know, influenza vaccine is unique because its active ingredients – the virus strains used to develop the vaccine – change almost every year.

Therefore, manufacturers must produce millions of doses of a new vaccine each year. While promising new technologies such as cell culture and recombinant protein and DNA-based vaccines are in the research and development stages and we are working with our HHS colleagues to advance their development, the most efficient vaccine production methods currently available involve the use of millions of live, non-sterile eggs to grow three different strains of influenza viruses annually. This is a complex process that spans several months where manufacturers cultivate the appropriate strains to make the vaccine. These factors present an enormous challenge for manufacturers and create uncertainty for vaccine supply.

Each year, FDA begins working with manufacturers at the earliest stages of vaccine development, and we continue to assist them throughout the production phase. We do this not only through our regulatory evaluations, but also by providing needed influenza strains that can be used for efficient manufacturing. Specifically, we provide reagents to assure that the vaccine is potent and further evaluate the vaccine through the use of laboratory tests that help assure the safety and efficacy of the vaccine. Throughout this process, FDA frequently discusses technical issues with manufacturers.

Influenza vaccine is highly cost-effective and beneficial to the public. Over the last decade, health care providers, the Centers for Disease Control and Prevention (CDC) and others have been very successful in expanding the

number of Americans who receive the vaccine. However, as we have emphasized in previous testimony before Congress, the influenza vaccine market is very fragile because the increasing demand has been coupled with a decline in the number of U.S-based and U.S. licensed manufacturers. Importantly, the market returns for producing this and many other vaccines are usually minimal while the financial and other risks involved are great. Further, vaccine manufacturing requires careful and comprehensive controls, a complex manufacturing process and highly specialized facilities that can be expensive to maintain and update. For the 2004-2005 season, only three U.S. licensed manufacturers began production of influenza virus vaccine: Chiron Corporation and Aventis Pasteur (renamed sanofi pasteur in December 2004) produced inactivated vaccine, the form currently used for most high-risk individuals, while MedImmune, Inc. manufactured FluMist, a recently approved live attenuated (weakened and safe) influenza vaccine.

As you know, on October 5, 2004, the British Medicines and Healthcare products Regulatory Agency (MHRA) suspended Chiron's license to manufacture influenza vaccine due to sterility failures in filled vials of the vaccine. FDA and MHRA's review of Chiron's investigation of the root causes of the company's sterility failures and our own review and inspections of their facility pointed to general problems that led FDA to the conclusion that the sterility, and therefore safety, of the vaccine Chiron produced for the 2004-2005 influenza season could not be assured.

Efforts to Obtain Additional Vaccine

The loss of Chiron's planned contribution to the U.S. influenza vaccine supply posed serious challenges. FDA worked with urgency, aggressiveness and in close coordination with CDC and other components of HHS and the private sector to explore all viable options to secure additional doses of influenza vaccine. FDA worked with sanofi pasteur and MedImmune to secure approximately five million additional doses of U.S. licensed vaccine. Sanofi pasteur increased production to 58 million doses of Fluzone, and MedImmune scaled up to produce three million doses of FluMist. FluMist is currently recommended for healthy individuals 5 to 49 years of age, and therefore provides an option for those who would not receive vaccine under CDC's priority guidelines, such as the U.S. military. Therefore, to expand further the supply of vaccine to those with the greatest need, Secretary Thompson, in cooperation with the Department of Defense, announced that the military would maximize its use of FluMist as a substitute to the inactivated vaccine, making an additional 200,000 doses of injectable vaccine available to HHS for high-risk civilian populations. Because sanofi pasteur produces pediatric dosage forms of vaccine for the U.S. market, the supply of vaccine available for high-risk children was, fortunately, not reduced. Through these collaborative efforts, manufacturers increased the available supply of licensed influenza vaccine for the U.S. population to 61 million doses for this influenza season, compared with

approximately 83 million doses distributed in 2003-2004 and in 2002-2003, 77 million doses in 2001-2002 and 70 million doses in 2000-2001.

Because there was a concern that the need and demand could still outstrip supply, particularly if we face a severe influenza season, we sought additional doses of vaccine that could be safely used in an emergency. Thus, in addition to enhancing the supplies of vaccine approved for use in the U.S., we were able to rapidly identify suppliers of approximately five million doses of additional vaccine, licensed in other countries, that could potentially be made available under an FDA investigational new drug (IND) application. With remarkable cooperation from several companies and from other regulatory agencies (including the Paul Ehrlich Institute, Germany; Therapeutic Goods Administration, Australia; Swiss Medic and Health Canada) FDA immediately sent inspectors and scientists to the manufacturing facilities of potential IND sponsors to evaluate their manufacturing processes. Coupled with these efforts, we also reviewed a large volume of manufacturing and clinical data, all within in a few weeks. These efforts resulted in FDA approving INDs that permitted the potential use of approximately four million doses from GlaxoSmithKline (GSK) and one million doses from Berna Biotech, if needed. Of the five million doses potentially available under an IND, FDA understands that CDC has purchased approximately 1.5 million doses. HHS and FDA's coordinated interactions with these and other influenza vaccine manufacturers and regulatory agencies also provided valuable information and strengthened relationships that we hope will help stimulate interest by additional

influenza vaccine manufacturers and potentially lead to successful U.S. licensure. This is one constructive outcome of the challenges we faced this flu season. I am very proud of the efforts and accomplishments of more than 50 FDA employees, from multiple offices, as well as our HHS and CDC colleagues, working collaboratively for long hours to help meet this public health challenge.

Efforts to Enhance Antiviral and Pneumococcal Vaccine Supplies

Following the loss of the Chiron vaccine, FDA contacted manufacturers worldwide in an effort to identify additional supplies of antiviral medications that could be used, if needed, for treatment of millions of influenza cases and for prevention in high-risk individuals in epidemic settings.

Serious morbidity and mortality from influenza is often due to the complication of bacterial pneumonia. In particular, pneumococcal pneumonia is one of the most important and common serious complications of influenza in high-risk individuals. This complication is, itself, preventable through use of an inexpensive, yet underutilized, vaccine. The influenza vaccine shortage provided an impetus to increase use of vaccine against pneumonia. In cooperation with HHS, Merck & Company tripled its production of its pneumococcal polysaccharide vaccine from 6 million to more than 17 million doses, and the availability of this expanded supply will help physicians and public health officials reduce the risk of this complication. The beneficial effects of pneumococcal vaccine last for five to ten years, and CDC and other public health agencies strongly encouraged its use.

PLANS FOR 2005 AND FUTURE YEARS

At the same time that we have addressed this past year's shortage by facilitating the availability of additional vaccine, antivirals, and pneumococcal vaccine, we are doing everything we can to improve supply for future years. We are taking a dual-track strategy.

First, the most important single factor that will determine the adequacy of the U.S. influenza vaccine supply for the coming year will be whether Chiron can correct its manufacturing problems at the Liverpool facility and supply vaccine for the U.S. market. To succeed in this, Chiron is proceeding with extensive improvements that must satisfy both FDA and the U.K. regulatory authority. MHRA would also have to lift its license suspension and allow export of vaccine, which it can do whenever Chiron's compliance with MHRA regulatory requirements is satisfactory. Therefore, FDA continues to interact intensively with Chiron as the company institutes its remediation plan. FDA and MHRA have collaboratively reviewed this plan and provided extensive feedback to the company, and we are continually evaluating Chiron's progress.

FDA and MHRA have also improved their respective information sharing, which has led to an enhanced ability for both regulators to monitor Chiron. We have come a long way since October 5, 2004, when MHRA could not legally communicate with FDA about its pending enforcement actions. FDA and MHRA

now have an agreement with Chiron that allows full sharing of information between FDA and MHRA, as the company works to address the problems in Liverpool. MHRA and FDA are in frequent communication, conducting frequent conferences by video or telephone to collaboratively share and review information and to evaluate and discuss Chiron's remediation activities. FDA and MHRA are also working together and actively communicating on inspectional activities. For example, FDA accompanied MHRA on a preliminary inspection of Chiron's Liverpool facility in late December. FDA will participate in the next MHRA inspection and continue to coordinate with and accompany MHRA on future inspections. FDA will continue to provide MHRA and Chiron with feedback and information. In the spring, at an appropriate time when all critical stages of manufacturing are in full swing, FDA plans to conduct a comprehensive inspection of Chiron's Liverpool facility to verify that Chiron has adequately addressed its problems. Only after passing MHRA and FDA inspections will Chiron be able to provide vaccine for the U.S. market. As the safety and efficacy of influenza vaccine is FDA's overwhelming concern, Chiron's vaccine will have to meet all required standards, including sterility and other safety testing, prior to distribution to the public. While it is too early to predict the outcome of Chiron's ongoing remediation activities, or MHRA's and FDA's regulatory decisions, Chiron appears to be making progress.

While working hard to facilitate Chiron's efforts to correct manufacturing problems, FDA is also simultaneously working on a second track to facilitate

greater diversification of the U.S. influenza vaccine supply. It is important to recognize, however, that demand for vaccine and other economic factors are, and will remain, the primary factors that determine whether a manufacturer will seek and maintain licensure, the strength of the manufacturing infrastructure in the U.S., and the amount of vaccine that manufacturers produce for the U.S. market. One important strategy is to encourage flu vaccination throughout the flu season, including January and February. To increase the total doses available, manufacturers can produce vaccine that becomes available during these months. Because influenza cases usually continue or peak well after the November-December time period when most people seek immunization, continuing vaccination is beneficial to recipients and should be encouraged. Also, while not a substitute for the protection of the following year's flu vaccination, this strategy may help provide added protection.

MedImmune has indicated that it is performing studies that, if successful, may support future use of its vaccine in additional age groups. They have also stated they have the capability to potentially produce as much as 40 million doses by 2007. Sanofi pasteur has indicated that it has the capability to produce the same or more doses of Fluzone for the 2005-2006 influenza season as it did in 2004-2005 but has not finalized its plans. Greater influenza vaccine production capacity and an increase in vaccination rates are critical for improving our preparedness for a global pandemic. In the event of a pandemic, we would need

the capacity to rapidly produce a new vaccine and make it available to all who need it.

While greater production by currently licensed manufacturers will enable us to meet some of these needs, recent events highlight the potential benefits of having more U.S. licensed manufacturers. In recognition of this, FDA has been doing everything possible to stimulate interested foreign licensed manufacturers to provide or, where needed, develop the safety and effectiveness data required to pursue U.S. licensure. FDA has interacted constructively with several interested firms in this regard. Where appropriate, FDA has informed manufacturers that it is willing to consider approaches to licensing such as accelerated approval based on likely surrogate markers (e.g. the degree of antibody response to the vaccine), followed by post-licensure clinical effectiveness evaluation. GSK has stated that it would like to use this approval mechanism and, thanks in part to clinical studies supported by the National Institute of Allergy and Infectious Diseases (NIAID), the company may be ready to seek accelerated approval of a new licensed influenza vaccine for the U.S. market in time for the 2005-2006 season.

Finally, we are doing all we can to have Chiron's and GSK's vaccines available to meet next year's needs. If difficulties arise, they should become apparent by summer and the experience and relationships built this year through reviewing

and obtaining vaccines licensed by other regulatory authorities will be helpful if needed to obtain additional vaccine for use under an IND.

OTHER IMPORTANT ACTIVITIES

We have challenged ourselves to identify other lessons learned from this year's influenza season and to examine how we can use our recent experience to help prevent similar problems in the future. For example, we have identified the need to share more information with our international regulatory counterparts, and vice versa. We have now completed confidentiality commitments that allow information sharing with regulatory agencies in Australia, Canada, the European Commission, Japan, Mexico, Switzerland, Singapore, and South Africa. We are also in final negotiations on agreements with the U.K. and New Zealand. In addition, we are conducting an ongoing inventory of foreign manufacturing to identify any additional needs for information sharing, and we plan to seek agreements with other national regulatory authorities, where necessary. These commitments help assure that legal barriers do not inhibit critical communication between these agencies and FDA.

CBER has also initiated a vulnerability analysis of foreign manufacturing of U.S. licensed products that are critical to U.S. public health. This analysis will cover influenza and other vaccines and help identify areas where consideration of actions to support supply may be needed, such as stockpiling or seeking

additional licensed manufacturers. In addition, in the hope that more vaccines can be licensed and available to multiple regions of the world, FDA has been working with our foreign regulatory counterparts and with manufacturers to encourage internationally harmonized and more efficient product development, and the development of scientific and regulatory standards for safety, potency and effectiveness that will help achieve these goals. FDA serves as a designated Collaborating Center of the World Health Organization (WHO), and we work closely with our sister agencies at HHS and WHO on pandemic preparedness and responding to other emerging infectious diseases.

Under FDA's Critical Path initiative, we are working collaboratively with HHS agencies and the private sector to facilitate the rapid development, evaluation and availability of medical products; and related manufacturing, safety and effectiveness standards. A good example of the effectiveness of this type of a collaborative public-private approach to public health product development to meet the threat of emerging infections was the rapid development and implementation of West Nile Virus screening for the blood supply.

As in past years, FDA will work closely with CDC, WHO and others to develop materials for standardization and evaluation of influenza vaccine for the 2005-2006 flu season. FDA will continue to identify and evaluate influenza virus strains suitable for manufacturing purposes, and provide the high growth

reassortant viruses to manufacturers that they need to help to facilitate efficient production of vaccine and a timely and adequate supply.

Recent events highlight the importance of FDA's technical support for the U.S. and global vaccine manufacturing infrastructure and the need for manufacturers to invest in more efficient, reliable and modern methods for producing influenza vaccine. With adequate supply and widespread immunization, we will be more likely to meet the challenge of annual influenza epidemics and future pandemics.

To help manufacturers overcome challenges such as the problems Chiron is experiencing, FDA, under its current Good Manufacturing Practice for the 21st Century initiative, is working with industry to encourage the use of advanced technologies as well as quality systems and risk-based approaches that build quality into the manufacturing process. FDA is also using the same quality systems and risk-based approaches to modernize its manufacturing-related regulatory responsibilities.

Recent experiences, particularly those of the past six months, have taught us important lessons about manufacturing and inspectional activities with respect to influenza vaccine. Although FDA has always interacted extensively with influenza vaccine manufacturers throughout the vaccine production cycle, the annual changes in the flu vaccine and the increased dependence on a smaller number of manufacturers highlight the risks of unexpected manufacturing

difficulties. For these reasons, in 2005 and the future, we plan to conduct inspections of influenza vaccine manufacturers on an annual basis, with additional interactions with manufacturers and, in the case of foreign facilities, their regulatory agencies where appropriate, based on findings or events that raise concerns.

PANDEMIC PREPAREDNESS

HHS is working together to help transform the influenza marketplace and reinvigorate influenza vaccine infrastructure by investing in promising new technologies, securing additional licensed vaccines and medicines and preparing stronger response plans and capacity. Furthermore, the lessons we have learned and insights gained from recent experiences with influenza vaccine are critical in preparing for an influenza pandemic. This is something that FDA and others in the public health community are very concerned about, given the eventual likelihood of a pandemic and the recent outbreaks of avian influenza in Asia. More widespread vaccination during periods between pandemics not only has direct health benefits but also will increase vaccine production capacity and help America and the global community better prepare for an influenza pandemic.

In response to the threat of an influenza pandemic, the continuing importance of influenza as a threat to public health, and the potential to continue to reduce

illness and death from influenza and its complications, the Administration made an initial pandemic preparedness investment of $50 million in fiscal year (FY) 2004. Congress provided $99 million for this activity in FY 2005. The President's budget for FY 2006 proposes a $21 million increase for this program, to $120 million. The Administration is making the largest investment ever made by the Federal government to protect against influenza. We welcome the continued support of Congress for this work, and view influenza preparedness as a critical responsibility as well as an important opportunity.

In August 2004, the Department released its draft Pandemic Influenza Preparedness and Response Plan. This draft document contains the basis for a coordinated national strategy to prepare for and respond to a pandemic.

Consistent with the draft plan, HHS continues to make progress in preparing to respond effectively to the next influenza pandemic. As one component of this preparedness, the Department has announced two Requests for Proposals designed to encourage U.S.-based influenza vaccine manufacturers to have both the capacity and raw materials necessary to produce large quantities of vaccine using current egg-based methods, which are efficient and have a long and generally successful history. In November 2004, HHS awarded a contract to sanofi pasteur to help ensure year round availability of an increased egg supply in case it is needed for a pandemic or for future vaccine shortages. These contracts and other research supported by HHS through NIAID will also help us

move from dependence solely on egg-based production technology to the development of domestically-produced U.S. licensed cell-culture based and/or recombinant protein and DNA-based vaccines. While work remains to obtain sufficient vaccine yields and evaluate cell-based vaccines for their safety and effectiveness, moving from an egg-based production to a cell-culture production can potentially shorten the time needed to produce vaccine as well as decrease the risk of contamination inherent in egg-based production.

In an important new development, HHS is supporting development of vaccines against potential pandemic strains. Through this effort we hope to obtain experience in the formulation and use of such a vaccine and to prepare in the event that these strains become pandemic. As part of HHS' efforts to support pandemic preparedness, NIAID contracted for the production of pilot lots of potential pandemic vaccines from the two licensed U.S. manufacturers of inactivated influenza vaccine. HHS contracted for the production of two million doses of vaccine against H5N1 avian flu, the influenza type of current concern in Southeast Asia. NIAID is preparing to initiate clinical studies of the first H5N1 vaccine under INDs that FDA oversees, and both agencies will be working together to evaluate the results. While much work remains, these steps to produce and evaluate pandemic influenza vaccines are a critical component of our preparedness efforts.

In addition, studies supported by the National Institutes of Health and FDA will try to develop vaccine strategies that could lead to longer lived immunity and to vaccines that help protect against multiple strains of influenza. FDA is actively engaged with sponsors and manufacturers that are interested in developing such new technologies and has approved cell-based and recombinant vaccines for prevention of other infectious diseases such as chicken pox, mumps, measles and hepatitis.

FDA's goal is to establish a process to produce pandemic influenza vaccine in the shortest amount of time possible and protect the largest number of people, using a vaccine that is safe, effective and easy to deliver. The full details of the draft Pandemic Influenza Preparedness and Response Plan are located on the HHS website at: *http://www.dhhs.gov/nvpo/pandemicplan/annex5.pdf*. Through all these efforts, and with enhanced global surveillance by CDC and its partners, we have the unique opportunity to effectively intervene and potentially blunt a global pandemic, should one occur.

CONCLUSION

HHS has announced that it plans to spend $439 million Department-wide on influenza related activities in FY 2006. This amount is an increase of nearly $400

million over the FY 2001 level of $41 million, and represents the Administration's commitment to addressing this important public health concern.

Although we may never completely prevent influenza outbreaks, with an adequate vaccine supply supplemented by effective antivirals we can greatly decrease our vulnerability and provide protection against influenza. FDA recognizes the need to work with multiple partners, including manufacturers, to increase supply and to support progress toward more modern, dependable methods of production. All of the steps we have discussed will not only help protect Americans from flu every year but will help prepare us for future influenza seasons or in the event pandemic strikes. We welcome the opportunity to work with manufacturers and Congress to accomplish these important public health goals.

Once again, thank you for inviting me to testify on this very important issue. I am happy to respond to your questions.